(FILE 'MEDLINE, CANCERLIT, EMBASE, BIOSIS, BIOTECHDS, CAPLUS' ENTERED AT 13:28:29 ON 01 AUG 2002)

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                DEL HIS
L1          72776 S ANTHRACENE
L2        1648352 S MUTA? OR HYPERMUTA? OR MISMATCH REPAIR
L3           5117 S L1 AND L2
L4       13402586 S CELL# OR MAMMAL OR RAT OR MURINE OR MOUSE OR IN VIVO
L5           3606 S L4 AND L3
L6           1669 DUP REM L5 (1937 DUPLICATES REMOVED)
L7           3791 S HYPERMUTAT?
L8              0 S L7 AND L6
L9         992579 S MUTAT?
L10          2871 S L9 AND L7
L11         12130 S MISMATCH REPAIR
L12           144 S L11 AND L10
L13           672 S L9 AND L6
L14             2 S L13 AND L11
L15           398 S L13 AND CELL
L16          4984 S 1,2-DIMETHYL
L17            47 S L16 AND L1
L18             8 S L17 AND L4
L19             6 DUP REM L18 (2 DUPLICATES REMOVED)
L20           399 S L6 AND ASSAY
L21            56 S L20 AND GENE

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L15 ANSWER 198 OF 398 CANCERLIT
AN 97600055 CANCERLIT
DN 97600055
TI P53 **mutations** in chemically induced hamster cheek-pouch tumors (Meeting abstract).
AU Gimenez-Conti I B; LaBate M; Liu F; Osterndorff E
CS Dept. of Carcinogenesis, Univ. of Texas M.D. Anderson Cancer Center, Science Park, Smithville, TX 78957.
SO Proc Annu Meet Am Assoc Cancer Res, (1996) 37 A804.
ISSN: 9017-016X.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199701
ED Entered STN: 19980417
Last Updated on STN: 19980417
AB To determine if and when p53 **mutations** occur in the development of squamous **cell** carcinoma (SCC), we studied alterations of this gene in the hamster cheek-pouch carcinogenesis model by using immunohistochemical staining and polymerase chain reaction-single-strand conformation polymorphism (PCR-SSCP) analysis followed by direct DNA sequencing. Twenty four hamsters were treated with 0.5% 7,12-dimethylbenz[a]**anthracene** in mineral oil three times a week for 16 wk. For this study, p53 protein accumulation was evaluated by immunostaining in various hamster cheek pouch lesions including exophytic and endophytic SCC as well as flat dysplastic hyperplasia and carcinomas in situ. A moderate percentage (33.3%) of exophytic lesions was negative for p53 staining, whereas most endophytic carcinomas (90%) showed positive p53 reaction. In addition we also found p53 positive staining in a number of flat lesions including areas of focal hyperplasia, dysplastic hyperplasia, and carcinomas in situ. To determine whether the alterations in p53 staining were due to p53 gene **mutation** we used PCR-SSCP and direct sequencing. PCR products corresponding to exons 5a, 6, 7, and 8 from p53-positive tumors showed shifted bands (four tumors in exon 5, two in exon 6, one in exon 7 and two in exon 8). Direct sequencing of some of the shifted bands revealed three **mutations**. Two of the **mutations** were transversions (G to T) in codons 216 and 252, and the third was a G to C transition in codon 282. This study and additional investigations of this suppressor gene in microdissected lesions may better define the mechanisms of carcinogenesis in the hamster cheek pouch model and may provide a new marker of progression for chemoprevention studies.

L15 ANSWER 197 OF 398 CANCERLIT
AN 97609652 CANCERLIT
DN 97609652
TI The specific N-ras **mutation** in **rat** 7,12-dimethylbenz[a]**anthracene** (DMBA)-induced leukemia (Meeting abstract).
AU Osaka M; Koh T; Matsuo S; Sugiyama T
CS Dept. Pathology and Tumor Biology, Postgraduate School of Medicine, Kyoto Univ., Kyoto, 606-01, Japan.
SO Non-serial, (1995) Leukemia and Lymphoma, Pathogenesis and Treatment, Molecular Aspects. 18th Symposium of the International Association for Competitive Research on Leukemia and Related Diseases, p. 62. Kyoto, Japan, October 29-November 3, 1995 .
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199705
ED Entered STN: 19980417
Last Updated on STN: 19980417
AB Intravenous injections of 7,12-dimethylbenz[a]**anthracene** (DMBA) induce erythroblastic leukemia (erythroleukemia) with 2 trisomy and Long 2 in Long-Evans rats. Recently, a consistent type of **mutation**, A to T transversion in codon 61 of N-ras gene, was found in all of 6 cultured leukemia **cell** lines and 9 primary leukemias induced by DMBA by polymerase chain reaction (PCR) and direct sequencing (Osaka et al, Cancer Lett; 91:25-31 1995.). On the contrary, no **mutation** was observed in Ha- and Ki-ras genes in all leukemias. The consistent occurrence of above N-ras **mutation** as well as in leukemias indicates that N-ras gene plays an important role in DMBA-leukemogenesis. **Mutations** in ras genes are considered to take place during the initiation stage of carcinogenesis because they often appear in the premalignant stage of tumors. In order to detect N-ras **mutation** in early stage of preleukemia, we designed the **mutant** -allele-specific amplification (MASA) method to detect the **mutation** in bone mamow (BM) **cells** of DMBA-treated rats. The MASA method was sensitive enough to detect one **mutant** among 10(6) normal **cells**. Using this method, the N-ras **mutation** was found in BM **cells** 2 days after single DMBA injection and thereafter throughout the preleukemic stage. These results suggest the importance of the N-ras **mutation** as an earliest event in DMBA-leukemogenesis.

L15 ANSWER 196 OF 398 CANCERLIT
AN 97619054 CANCERLIT
DN 97619054
TI Site-specific **mutagenesis** by bulky exocyclic amino-substituted guanine and adenine derivatives in E coli and human **cells**. (Meeting abstract).
AU Moon K-Y; Pauly G T; Moschel R C
CS ABL-BRP, NCI-FCRDC Frederick, MD 21702.
SO Proc Annu Meet Am Assoc Cancer Res, (1997) 38 A261.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199709
ED Entered STN: 19980417
Last Updated on STN: 19980417
AB The **mutagenicity** of the two major DNA adducts produced by 7-bromomethylbenz[a]-**anthracene** i.e., N2-(benz[a]anthracen-7-ylmethyl)-2'-deoxyguanosine (b[a]a2G) and N6-(benz[a]anthracen-7-ylmethyl)-2'-deoxyadenosine (b[a]a6A) as well as the simpler benzylated analogs N2-benzyl-2'-deoxyguanosine(bn2G) and N6-benzyl-2'-deoxyadenosine (bn6A) was examined in both E. coli and Ad293 human **cells**. In our E. coli site-specific **mutagenesis** system none of these aralkylated adducts exhibited any significant **mutagenicity** with or without SOS induction. In our human **cell** site-specific **mutagenesis** system bn2G and bn6A exhibited weak **mutagenicity** although b[a]a2G and b[a]a6A were significantly **mutagenic**. At the site of the adduct b[a]a2G produced G to T transversion **mutations** while b[a]a6A produced A to G transition **mutations**. These results indicate that the more bulky b[a]a2G and b[a]a6A exhibit significantly greater **mutagenicity** in human **cells** than in E. coli and further emphasize the importance of studying site-specific **mutagenesis** by carcinogen-modified DNA bases in human **cells**.

L15 ANSWER 192 OF 398 MEDLINE
AN 76051128 MEDLINE
DN 76051128 PubMed ID: 1186764
TI Mammalian **cell** transformation and **cell**-mediated **mutagenesis** by carcinogenic polycyclic hydrocarbons.
AU Huberman E
SO MUTATION RESEARCH, (1975 Aug) 29 (2) 285-91.
Journal code: 0400763. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197601
ED Entered STN: 19900313
Last Updated on STN: 19900313
Entered Medline: 19760123
AB The introduction of a polycyclic hydrocarbon such as benzo(alpha)pyrene (BP) into normal golden hamster embryo **cell** cultures results, in addition to cytotoxicity, in malignant **cell** transformation. Studies on the effect of different doses of BP on the normal **cells** showed that the frequency of transformed colonies was directly related to the dose of the carcinogen. Analysis of this dose-response curve suggests a one-event ("one-hit") response for transformation by this carcinogen. The one-event response for transformation by carcinogenic polycyclic hydrocarbons and the fact that these carcinogens bind to DNA in susceptible **cells** suggests that transformation can involve a single alteration in the genetic constitution of the treated **cells**. Carcinogens may, therefore, produce somatic **mutations**, some of which may involve the genes that control malignancy. Recently, considerable progress has been made in developing models for the study of chemical **mutagenesis** in mammalian **cells**. Using resistance to 8-azaguanine as a marker, positive correlations between **mutagenicity** and transformation were obtained with chemically reactive carcinogens such as N-acetoxy-N-2-fluorenyl-acetamide, N-methyl-N'-nitro-N-nitrosoguanidine and K-region epoxides of polycyclic hydrocarbons. However, no such correlations were obtained with the carcinogenic polycyclic hydrocarbons themselves, since the **cell** lines used in chemical **mutagenesis** do not metabolize these carcinogens. In order to obtain better correlations, we have developed a **cell**-mediated **mutagenic** assay with carcinogenic hydrocarbons in which Chinese hamster **cells**, which are susceptible for **mutagenesis**, were co-cultivated with lethally irradiated rodent **cells** that can metabolize these compounds. Using this **cell** mediated assay, we obtained **mutagenesis** with the carcinogenic hydrocarbons 7,12-dimethylbenz(alpha) **anthracene** (DMBA), BP, 3-methylcholanthrene and 7-methylbenz(alpha)**anthracene**; the most potent carcinogen, DMBA, gave the highest frequency of **mutations**. The polycyclic hydrocarbons, pyrene and benz(alpha)**anthracene**, which are not carcinogenic were also not **mutagenic**. We have therefore demonstrated a relationship between the carcinogenecity of polycyclic hydrocarbons and their **mutagenicity** in mammalian **cells**, without having to isolate their reative metabolic intermediates. It should be possible to use in this system human **cells** from different organs and individuals to screen for environmental chemicals hazardous to humans which have to be metabolically activated.

L15 ANSWER 185 OF 398 MEDLINE
AN 77206380 MEDLINE
DN 77206380 PubMed ID: 873646
TI The metabolic activation of 7-methylbenz(a)**anthracene**: the induction of malignant transformation and **mutation** in mammalian **cells** by non-K-region dihydrodiols.
AU Marquardt H; Baker S; Tierney B; Grover P L; Sims P
SO INTERNATIONAL JOURNAL OF CANCER, (1977 Jun 15) 19 (6) 828-33. Journal code: 0042124. ISSN: 0020-7136.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 197708
ED Entered STN: 19900314
Last Updated on STN: 19900314
Entered Medline: 19770812
AB Four different dihydrodiols derived from 7-methylbenz(a)**anthracene** have been tested, together with the parent hydrocarbon, for their ability to induce the in vitro malignant transformation of **mouse** M2 fibroblasts and **mutations** in V79 Chinese hamster **cells** . In the transformation tests withe the non-K-region dihydrodiols, the 3,4-diol was the most active dihydrodiol tested and the 8,9-diol was also more active than 7-methylbenz(a)**anthracene** itself; the 1,2-diol showed only slight activity. The K-region dihydrodiol, the 5,6-diol, which cannot be directly metabolized to a vicinal diol-epoxide, was inactive. These differences in biological activity were similar to those apparent in the results from the **mutagenicity** tests. The data support the general hypothesis that non-I-region dihydrodiols, which can be metabolized to vicinal diol-epoxides, are important in the metabolic activation of the carcinogenic polycyclic hydrocarbons and, when taken together with other results, indicate that 3,4-dihydro-3,4-dihydroxy-7-methylbenz(a)**anthracene** is most probably involved in the metabolic activation of 7-methylbenz(a)**anthracene** presumably following conversion into the related diol-epoxide, 3,4-dihydro-3,4-dihydroxy-7-methylbenz(a)**anthracene** 1,2,-oxide.

L15 ANSWER 186 OF 398 MEDLINE

L15 ANSWER 178 OF 398 MEDLINE

AN 80176968 MEDLINE

DN 80176968 PubMed ID: 6768455

TI Mammary gland **cell**-mediated **mutagenesis** of mammalian **cells** by organ-specific carcinogens.

AU Gould M N

SO CANCER RESEARCH, (1980 Jun) 40 (6) 1836-41.
Journal code: 2984705R. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Priority Journals

EM 198007

ED Entered STN: 19900315
Last Updated on STN: 19900315
Entered Medline: 19800726

AB **Rat** mammary gland **cells** have been used to activate chemical procarcinogens to **mutagenic** compounds in a culture system. **Mutagenesis** was tested in Chinese hamster V-79 **cells** that were cocultured with the mammary **cells**. The locus **mutations** tested for were resistance to ouabain and resistance to 6-thioguanine. Mammary **cells** were separated into several fractions. Fractions enriched in either epithelial or stromal **cells** could both mediate **mutagenesis**. The **mutation** frequency related to the density of the mammary **cells**. The mammary carcinogen 7, 12-dimethylbenz(a) **anthracene** exhibited a dose-dependent enhancement of **mutation** frequency and cytotoxicity when added to the cocultures, whereas the hepatocarcinogen aflatoxin B1 did not. This system may be useful in examining some of the mechanisms of organ-specific carcinogenesis and also may act as a screening system for carcinogenic environmental contaminants.

L15 ANSWER 179 OF 398 MEDLINE

L15 ANSWER 173 OF 398 MEDLINE
AN 82048943 MEDLINE
DN 82048943 PubMed ID: 6271413
TI Lung and liver **cell**-mediated **mutagenesis** systems: specificities in the activation of chemical carcinogens.
AU Langenbach R; Nesnow S; Tompa A; Gingell R; Kuszynski C
NC 5-R01-CA20022 (NCI)
SO CARCINOGENESIS, (1981) 2 (9) 851-8.
Journal code: 8008055. ISSN: 0143-3334.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198201
ED Entered STN: 19900316
Last Updated on STN: 19970203
Entered Medline: 19820109
AB A liver and lung **cell**-mediated-V79 **cell** **mutagenesis** system using intact **cells** as metabolic activation systems was employed to study the relative ability of **cells** from these organs to activate chemical carcinogens. Primary cultures of liver and lung **cells** from male Sprague Dawley rats were used to metabolically activate the chemicals and the **mutation** of Chinese hamster V79 **cells** to ouabain resistance used to detect **mutagenic** intermediates. 7,12-Dimethylbenz[a] **anthracene** and 3-methylcholanthrene, were more active in the lung system than in the liver **cell** system. Benzo[a]pyrene (B[a]P) was inactive in the liver **cell**-mediated system but **mutagenic** to V79 **cells** in the lung **cell**-mediated system. Dimethylnitrosamine (DMN) was inactive in the presence of liver **cells**. Aflatoxin B1 was **mutagenic** in the liver **cell**-mediated system, but only weakly **mutagenic** in the lung **cell**-mediated system. Because the **mutagenicities** of DMN and B[a]P were organ-specific, the metabolism of these carcinogens in the two primary **cell** systems was investigated. DMN was metabolized by liver but not by lung **cells**, possibly accounting for its lack of **mutagenicity** in the lung **cell** system. B[a]P was extensively metabolized by both **cell** types, but quantitative differences were observed when the metabolic products were analyzed by high pressure liquid chromatography. Comparing total organic and water soluble metabolites, lung **cells** produced similar amounts of 7,8- and 9,10-diols but little 4,5-diol, while liver **cells** produced equivalent total amounts of the three diols. Lung **cells** produced twice the amount of B[a]P glucuronide conjugates as liver **cells**, while liver **cells** produced twice the amount of B[a]P sulfate conjugates as lung. The data suggest that intact **cells** from various organs can be used as metabolic activating systems in vitro assays and that studies into organ specificity can be investigated by this approach.

L15 ANSWER 161 OF 398 MEDLINE
AN 83177994 MEDLINE
DN 83177994 PubMed ID: 6838477
TI The use of DNA-repair-deficient **mutants** of Chinese hamster ovary **cells** in studying **mutagenesis** mechanisms and testing for environmental **mutagens**.
AU Thompson L H
SO BASIC LIFE SCIENCES, (1983) 23 217-46.
Journal code: 0360077. ISSN: 0090-5542.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198305
ED Entered STN: 19900318
Last Updated on STN: 19900318
Entered Medline: 19830505
AB Our laboratory has taken a somatic-**cell**-genetics approach to the study of **mutagenesis** by utilizing **mutant** strains of Chinese hamster ovary (CHO) **cells** that are deficient in DNA repair processes. From more than 150 UV-sensitive strains tested, five complementation classes were identified, and representative **mutants** were found to be defective at, or before, the incision step of excision repair. A representative **mutant**, strain UV-5, was compared with the parental strain in terms of cytotoxicity and dose-response curves for **mutation** induction after treatment with UV and several chemicals that are known to produce large adducts in DNA. Excision repair in normal CHO **cells** protects against both cytotoxicity and **mutagenesis**, but the degree of protection depends on both the agent and the genetic marker used for detecting **mutations**. Upon treatment with low doses (100% **cell** survival) of the polyaromatic hydrocarbon 7-bromomethylbenz(a) **anthracene**, repair-deficient UV-5 **cells** had linear responses for **mutation** induction to thioguanine resistance or azaadenine resistance, whereas the normal repair-proficient **cells** showed curvilinear responses in which the slope increased with dose. This behavior suggests that in the normal **cells** the repair system acting on potentially **mutagenic** lesions becomes saturated at doses that produce cytotoxicity. In no instance was a lower **mutation** frequency induced in UV-5 **cells** than the parental **cells**, at a given dose of **mutagen**, suggesting that the excision repair system is error-free in normal CHO **cells**

L15 ANSWER 152 OF 398 MEDLINE
AN 84093273 MEDLINE
DN 84093273 PubMed ID: 6656796
TI Hypersensitivity to **cell** killing and **mutation** induction by chemical carcinogens in an excision repair-deficient **mutant** of CHO **cells**.
AU Thompson L H; Salazar E P; Brookman K W; Hoy C A
SO MUTATION RESEARCH, (1983 Dec) 112 (6) 329-44.
Journal code: 0400763. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198402
ED Entered STN: 19900319
Last Updated on STN: 19900319
Entered Medline: 19840214
AB A strain of Chinese hamster ovary **cells** that is deficient in nucleotide excision repair, strain UV5, was compared with the normal parental CHO **cells** in terms of cytotoxicity and **mutagenesis** after exposure to several chemical carcinogens that are known to produce bulky, covalent adducts in DNA. Induced **mutations** were measured at the hprt locus using thioguanine resistance and at the aprt locus using azaadenine resistance. The compounds tested that required metabolic activation (using **rat** or hamster microsomal fractions) were 7,12-dimethylbenz(a) **anthracene**, 3-methylcholanthrene, benzo(a)pyrene, aflatoxin B1, 2-acetylaminofluorene, and 2-naphthylamine. The direct-acting compounds (+/-)-r-7,t-8-dihydroxy-t-9,10-epoxy-7,8,9,10-tetrahydrobenzo(a)pyrene, N-acetoxy-2-acetylaminofluorene, and N-OH-2-naphthylamine were also studied. For all compounds except 2-naphthylamine and its active metabolite, the repair-deficient **cells** were significantly more sensitive to killing than the normal CHO **cells**. **Mutation** induction at both loci was also more efficient in UV5 **cells** in each instance where enhanced cytotoxicity was observed. By using tritium-labeled N-acetoxy-2-acetylaminofluorene, normal and **mutant** **cells** were shown to bind **mutagen** to their nuclear DNA with similar efficiency, and a greater amount of adduct removal occurred in the normal **cells**. From this study it is concluded that the use of excision repair-deficient CHO **cells** provides enhanced sensitivity for detecting **mutagenesis** and that a positive differential cytotoxicity response gives an indication of repairable, potentially lethal genetic damage.

L15 ANSWER 123 OF 398 MEDLINE
AN 88079999 MEDLINE
DN 88079999 PubMed ID: 3121168
TI Development of **murine** epidermal **cell** lines which contain an activated rasHa oncogene and form papillomas in skin grafts on athymic nude **mouse** hosts.
AU Strickland J E; Greenhalgh D A; Koceva-Chyla A; Hennings H; Restrepo C; Balaschak M; Yuspa S H
CS Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, Bethesda, Maryland 20892.
SO CANCER RESEARCH, (1988 Jan 1) 48 (1) 165-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 198802
ED Entered STN: 19900305
Last Updated on STN: 19900305
Entered Medline: 19880208
AB We have developed four **murine** epidermal **cell** lines which form squamous papillomas when grafted to athymic nude mice in a reconstituted skin. Two of the lines, SP-1 and BP-4, were derived from pools of papillomas produced on SENCAR and BALB/c **mouse** skin, respectively, by initiation with 7,12-dimethylbenz(a)**anthracene** and promotion with 12-O-tetradecanoylphorbol-13-acetate. Line 308 was derived from BALB/c **mouse** skin initiated in **vivo** with 7,12-dimethylbenz(a)**anthracene**, culture of the epidermal **cells**, and selection of **cells** resistant to Ca2+-induced terminal differentiation. Line LC14 was derived from untreated, cultured newborn BALB/c **mouse** primary epidermal **cells** which spontaneously developed resistance to Ca2+-induced terminal differentiation. Each line has an activated rasHa gene with a **mutation** within codon 61. **Cells** from all four lines, in contrast to normal primary epidermal **cells**, survive in medium with Ca2+ levels greater than 0.1 mM. Clonal growth studies in culture showed a unique growth pattern for each of the four lines in medium with 1.4 mM and 0.05 mM Ca2+, with or without 12-O-tetradecanoylphorbol-13-acetate. Early passage **cells** of these lines should provide a valuable resource for detecting genes or genetic alterations which complement an activated ras gene to cause malignant conversion and for studying the biology of tumor promotion.

tumor and suggest that it could be involved in tumor regression.

L15 ANSWER 104 OF 398 MEDLINE
AN 91058635 MEDLINE
DN 91058635 PubMed ID: 1978778
TI Ha-ras oncogene **mutations** in **cell** lines derived from **rat** tracheal implants exposed in **vivo** to 7,12-dimethylbenz[a]**anthracene**.
AU Cosma G N; Wirgin I I; Marchok A C; Garte S J
CS Institute of Environmental Medicine, New York University Medical Center, New York 10016.
NC CA13343 (NCI)
CA36342 (NCI)
CA42798 (NCI)
+
SO MOLECULAR CARCINOGENESIS, (1990) 3 (5) 258-63.
Journal code: 8811105. ISSN: 0899-1987.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199101
ED Entered STN: 19910222
Last Updated on STN: 20000303
Entered Medline: 19910110
AB The frequency of Ha-ras **mutations** was determined as a function of neoplastic progression in **cell** lines derived from **rat** tracheal implants exposed in **vivo** to 7,12-dimethylbenz[a] **anthracene**. Restriction fragment-length polymorphism (RFLP) analysis revealed an A----T transversion in the second base of codon 61 in 2 of 11 **cell** lines. One of the positive **cell** lines was tumorigenic, but the other was neither tumorigenic nor anchorage independent, thus indicating a lack of correlation between neoplastic stage and ras **mutation**. Densitometry analysis of the RFLP bands indicated that approximately 50% of the **cells** within these two heterogeneous populations contained the **mutation**. Direct sequence analysis of polymerase chain reaction-amplified DNA confirmed these results and did not reveal any other **mutations** in this region of the Ha-ras gene.

L19 ANSWER 1 OF 6 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 93208547 EMBASE
DN 1993208547
TI **1,2-Dimethyl**-9, 10 benzanthracene induced malignant fibrous histiocytoma in rats and the effect of adrenalectomy on tumor growth.
AU Kotiloglu E.; Oner U.
CS Pediatric Pathology Unit, Hacettepe University Medical School,Ankara, Turkey
SO Doğa - Turkish Journal of Medical Sciences, (1993) 18/2 (115-126).
ISSN: 1010-7584 CODEN: DTJSEX
CY Turkey
DT Journal; Article
FS 005 General Pathology and Pathological Anatomy
016 Cancer
052 Toxicology
LA English
SL English

L19 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2002 ACS
AN 1993:249623 CAPLUS
DN 118:249623
TI Comparison of target organs of carcinogenicity for mutagenic and non-mutagenic chemicals
AU Gold, Lois Swirsky; Slone, Thomas H.; Stern, Bonnie R.; Bernstein, Leslie
CS Life Sci. Div., Lawrence Berkeley Lab., Berkeley, CA, 94720, USA
SO Mutat. Res. (1993), 286(1), 75-100
CODEN: MUREAV; ISSN: 0027-5107
DT Journal
LA English
AB A comparison of target organs for mutagens and non-mutagens is presented for 351 rodent carcinogens in the Carcinogenic Potency Database (CPDB) with mutagenicity evaluations in Salmonella. Results are consistent with the hypotheses that in high-dose rodent tests mitogenesis is important in the carcinogenic response for mutagens and non-mutagens alike, and that mutagens have a multiplicative interaction for carcinogenicity because they can both damage DNA directly and cause **cell** division at high doses. Among carcinogens that induce tumors at multiple sites in both rats and mice, 81% are mutagens; in comparison, among carcinogens that are pos. at only a single target site in one species and are neg. in the other, 42% are mutagens. Both mutagens and non-mutagens induce tumors in a wide variety of sites, and most organs are target sites for both. Moreover, the same sites tend to be the most common sites for both: 79% or more of both mutagenic and non-mutagenic carcinogens are pos. in each species in at least one of the 8 most frequent target sites: liver, lung, mammary gland, stomach, vascular system, kidney, hematopoietic system and urinary bladder. Species differences are discussed as well as results for particular target organs: liver, Zymbal's gland and kidney. A compendium of bioassay results is presented.

L21 ANSWER 46 OF 56 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
AN 2001:276690 BIOSIS
DN PREV200100276690
TI In vitro and in **vivo** chemopreventive properties of a soybean peptide (lunasin.
AU Lam, Yi (1); Chen, Na (1); de Lumen, Benito (1)
CS (1) University of California, Berkeley, CA USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A281. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Lunasin is a non-abundant 43-amino acid peptide found in soybean and contains an -RGD-**cell** adhesion motif followed by 8 aspartic acid (D) residues at the carboxyl end. Previous studies have demonstrated the ability of lunasin to bind to chromatin, leading to disruption of kinetochore formation and inhibition of mitosis when the lunasin **gene** is transfected into mammalian **cells**. Experiments reported here indicate that lunasin peptide can inhibit carcinogenesis both in **vivo** and > in vitro. We studied the effect of topically applied lunasin in a two-stage protocol of skin carcinogenesis in female SENCAR mice. At 13 weeks of age mice were initiated with 5 mug 7,12-dimethylbenz(a)**anthracene** (DMBA), and promoted with 2 mug 12-O-tetradecanoylphorbol-13-acetate (TPA) twice per week for 19 weeks. Starting from the week prior to DMBA administration till the end of the study, mice were subjected to 2.5 mug, 25 mug or 250 mug of lunasin peptide applied topically in 100% ethanol weekly. A significant reduction in tumor incidence and tumor latency was observed in the high-dosage (250 mug/week) lunasin group but not in the low (2.5 mug/week) and medium (2.5 mug/week) dosage groups. These results demonstrate that high dosage of lunasin is effective in inhibiting skin carcinogenesis and this effect could have been exerted during the initiation or the promotion stages. Lunasin peptide has also been shown to suppress ras induced transformation of **mouse** fibroblast NIH 3T3 **cells** in vitro by 40% at a concentration as low as 100nM. Lunasin had an irreversible effect on ras-transformation process since treatment with lunasin for 3 days was effective in suppressing transformation. Lunasin can suppress foci formation even when added 7 days after ras transfection of 3T3 **cells**. Using various deletion **mutant** forms of lunasin in the foci **assay**, we found that the polyaspartic end of lunasin is necessary for the transformation suppression effect. Furthermore lunasin reduced anchorage independent growth of stably ras-transfected **mouse** fibroblast **cells** by 40% in a colony formation **assay**. In addition, Western analyses show that lunasin increases p21 expression in ras-transfected **cells**.

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@PJL USTATUS DEVICE = ON
@PJL USTATUS TIMED = 30
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L21 ANSWER 28 OF 56 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
AN 2001158665 EMBASE
TI Promoting effect of a high-fat/high-protein diet in DMBA-induced ductal pancreatic cancer in rats.
AU Z'graggen K.; Warshaw A.L.; Werner J.; Graeme-Cook F.; Jimenez R.E.; Fernandez-del Castillo C.; Urist M.M.; Townsend C.M. Jr.; Warshaw A.L.
CS Dr. C. Fernandez-del Castillo, Department of Surgery, Massachusetts General Hospital, WACC 336, Boston, MA 02114, United States
SO Annals of Surgery, (2001) 233/5 (688-695).
Refs: 21
ISSN: 0003-4932 CODEN: ANSUA5
CY United States
DT Journal; Conference Article
FS 009 Surgery
016 Cancer
029 Clinical Biochemistry
LA English
SL English
AB Objective: To investigate whether a high-fat/high-protein diet (HFPD) acts as a promoter of the natural course of cancer growth in the 7,12-dimethylbenzanthracene (DMBA)-induced ductal pancreatic cancer model in rats. Summary Background Data: DMBA implantation to the **rat** pancreas induces ductal adenocarcinoma. Information regarding the effects of diet and the presence of K-ras **mutation** in this model is not available. Methods: Rats were randomly assigned to regular **rat** chow or a diet with a 30% content in fat and protein (HFPD). The presentation of cancer, the histologic spectrum of neoplasia at 1 and 9 months, and the prevalence of cancer in relation to diet were assessed. Histologic specimens comprising normal ducts, hyperplasia, dysplasia/carcinoma in situ, or carcinoma were designated by a pathologist and microdissected. Genomic DNA was extracted, and K-ras and H-ras **gene mutations** were determined by a **mutant** -enriched polymerase chain reaction **assay** and direct sequencing. Results: Rats fed HFPD increased their weight significantly compared with controls. DMBA induced characteristic stages of neoplasia at the implant site but not elsewhere. Macroscopic cancers of the pancreatic head presented regularly with common bile duct and gastric outlet obstruction. The prevalence of K-ras **mutations** was proportional to the degree of epithelial abnormality. K-ras **mutations** were significantly more frequent in cancer than in normal and hyperplastic ducts. H-ras **mutations** were not found. At 1 month in the HFPD-fed rats, the prevalence of cancer (16%) and dysplasia (16%) was not significantly different from the prevalence of cancer (29%) and dysplasia (8%) in the chow-fed rats. At 9 months the prevalence of cancer in the HFPD-fed rats increased to 29%, whereas that in the chow-fed rats decreased to 17%. The combined prevalence of cancer and dysplasia at 9 months in the HFPD-fed rats (34%) significantly exceeded that in the chow-fed rats. Conclusions: DMBA induces characteristic stages of neoplasia in the evolution of ductal pancreatic cancer in rats. K-ras **mutations** occur progressively in the ladder of oncogenesis, as in human pancreatic neoplasms. The addition of a diet with a high fat and protein content acts as a promoter of carcinogenesis, possibly by interfering with repair mechanisms and natural regression of early lesions.

L21 ANSWER 26 OF 56 CANCERLIT
AN 88643618 CANCERLIT
DN 88643618
TI ACTIVATION OF RAS ONCOGENES BY CHEMICAL CARCINOGENS.
AU Barbacid M; Sukumar S; Zarbl H
CS Developmental Oncology Section, LBI-Basic Res. Program, NCI-Frederick Cancer Res. Facility, P.O. Box B, Building 539, Frederick, MD.
SO Gene Amplification Anal, (1986) 4 21-38.
ISSN: 0275-2778.
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Institute for Cell and Developmental Biology
EM 198805
ED Entered STN: 19941107
Last Updated on STN: 19950508
AB Data from the authors' and others' laboratories pertaining to the mechanism of activation and involvement of ras oncogenes in human and carcinogen-induced animal tumors are reviewed. High proportions (79% and 72%, respectively) of N-nitroso-N-methylurea (NMU)-induced mammary carcinomas contained H-ras-1 oncogenes in experiments with Buf/N or Sprague-Dawley rats. A polymorphic Mnl I DNA fragment was generated and used in a **gene** transfer **assay** for the presence of **mutated** H-ras-1 **gene**. Altogether, 61/71 NMU-induced tumors scored positive in the Mnl I **assay**, including 32/61 for Buf/N and 23/61 for Sprague-Dawley. Of these 55 mammary carcinomas known to contain H-ras-1 oncogenes by molecular assays, only 48 (30 Buf/N and 18 Sprague-Dawley) scored positive in **gene** transfer assays. These observations suggest a close association between **mutagenesis** in this specific polymorphic Mnl I fragment of the H-ras-1 locus and tumor development. Nonadecamers were generated that were capable of identifying substitutions in position 35 (specific point **mutations**) in genomic DNA. This residue is the only nucleotide of the Mnl I cleavage site that can alter the coding properties of the critical twelfth codon of the H-ras-1 **gene**. With this system, the presence of activating deoxyguanosine to deoxyadenosine or deoxythymidine **mutations** of H-ras-1 oncogenes was demonstrated unequivocally in DNA isolated from tumor tissues. Using a nonadecamer probe complementary to the 61st codon (CAA) and flanking sequences of the normal **rat** H-ras-1 locus, it was shown that each of the five H-ras-1 oncogenes present in 7,12-dimethylbenz(a)**anthracene**-induced mammary carcinomas harbored **mutations** in the region of the 61st codon. It was further demonstrated that the G to A **mutations** present in each of the NMU-induced H-ras-1 oncogenes do not result from either positive growth selection or specific repair systems. Instead, the malignant activation of the H-ras-1 locus in NMU-induced mammary carcinomas results from the direct **mutagenic** effect of NMU on this locus. It is very likely that some environmental carcinogens might initiate human tumors by activating ras oncogenes. (50 Refs)

L21 ANSWER 24 OF 56 CANCERLIT
AN 94697099 CANCERLIT
DN 94697099
TI N-methyl-N-nitrosourea induced **rat** mammary tumors arise from **cells** harboring spontaneous oncogenic Ha-ras-1 **gene mutations**.
AU Cha R S
CS Massachusetts Institute of Technology.
SO Diss Abstr Int [B], (1993) 54 (3) 1363.
ISSN: 0419-4217.
DT (THESIS)
LA English
FS Institute for Cell and Developmental Biology
EM 199405
ED Entered STN: 19941107
Last Updated on STN: 19970509
AB The overall goal of this project was to directly measure the number of **cells** harboring the specific oncogenic **mutations** in target tissues of animals before and after carcinogen exposure. The NMU-induced **rat** mammary tumor model was chosen. The direct measurements of the specific ras **mutants** in animal tissues required the development of a polymerase chain reaction (PCR)-based procedure (mismatch amplification **mutation assay** or MAMA) which could detect the G-to-A transitions at the 12th codon of the Ha-ras **gene** present at a frequency of 10(-5). This procedure was then applied in measuring the number of specific ras **mutants** in the mammary epithelium before and after NMU exposure. Based on these results, it was concluded that the NMU-induced mammary tumors carrying the specific Ha-ras **gene mutations** arose from pre-existing ras **mutants**. Presumably, an independent effect(s) of NMU in one of these **mutant cells** was responsible for tumor formation. In an attempt to investigate molecular mechanisms underlying tissue specificity in NMU-induced tumorigenesis, MAMA was also carried out on the nontarget liver tissue before and after NMU exposure. These results were then compared to the results obtained from mammary tissue. These observations suggest that the lower **mutation** rate for the specific G-to-A transitions of the Ha-ras **gene** and the fact that the ras **mutants** do not acquire a significant growth advantage in the liver tissue may contribute to the apparent resistance of liver tissue to NMU-induced tumorigenesis. Molecular analysis of NMU- and dimethylbenz(a)**anthracene** (DMBA)-induced, and spontaneously arising mammary lesions was carried out utilizing denaturant gradient gel electrophoresis. None of the 31 spontaneously arising mammary lesions carried activated Ha-ras genes. These results suggest that the pre-existing ras **mutants** are specifically promoted during NMU-induced tumorigenesis, but not during DMBA-induced, or spontaneous tumorigenesis. The conspicuous absence of this G-to-A **mutation** among DMBA-induced and spontaneously arising mammary lesions suggest that independent molecular mechanisms are responsible for development of mammary lesions in these systems. (Copies available exclusively from MIT Libraries, Rm. 14-0551, Cambridge, MA 02139-4307. Ph. 617-253-5668; Fax 617-253-1690. Abstract shortened by UMI. Not available from University Microfilms Int'l.)

L21 ANSWER 23 OF 56 CANCERLIT
AN 96604700 CANCERLIT
DN 96604700
TI Carcinogen induced mechanisms in mammary tumorigenesis (Meeting abstract).
AU Jin Z; Zarbl H
CS Fred Hutchinson Cancer Research Center, Seattle, WA 98104-2092.
SO Proc Annu Meet Am Assoc Cancer Res, (1995) 36 A658-9.
ISSN: 0197-016X.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199605
ED Entered STN: 19970509
Last Updated on STN: 19970509
AB We developed a Mismatch Amplification **Mutation Assay** (MAMA) capable of detecting codon twelve GGA to GAA **mutations** in the Ha-ras-1 **gene** when present at a frequency of one in 10(5) alleles. The MAMA was used to measure the frequency of the activating Ha-ras-1 **gene mutation** in mammary epithelial **cells** (RMECs) of 50 day old, virgin, female Fischer 344 rats, before and after exposure to a single carcinogenic dose of N-nitroso-N-methylurea (NMU). The codon twelve G to A transitions arose as background **mutations** in the developing mammary gland and Ha-ras **mutants** were clustered within organ sectors, consistent with their origin during mammary gland development. Exposure to a single carcinogenic dose of NMU failed to induce a significant increase in the number of Ha-ras-1 **mutants**, the fraction of organ sectors containing **mutant cells**, or the fraction of animals harboring mammary epithelial **cells** with Ha-ras-1 **gene mutations**. Thus, the vast majority of NMU-induced carcinomas arise from mammary epithelial **cells** which harbored Ha-ras-1 oncogenes prior to carcinogen exposure. Our results further indicated that NMU allows for the outgrowth of pre-existing Ha-ras-1 **mutants**, and that one or more of these clones eventually gives rise to mammary carcinomas. Although the target for NMU-induced **mutagenesis** could be composed of a large set of cooperating oncogenes or tumor suppressor genes, it was equally plausible that the carcinogenic effect of NMU is mediated via nonmutagenic mechanisms. We used Southern blot analyses of genomic DNAs digested with either the HpaII or MspI restriction enzymes (methylation sensitive and insensitive isoschizomers, respectively) to detect changes in Ha-ras-1 **gene** DNA methylation after treatment of rats with NMU. While these studies failed to detect any NMU-induced changes in Ha-ras-1 **gene** methylation, they did reveal the presence of a HpaII/MspI restriction site within the Ha-ras-1 promoter region of DNA isolated from RMECs which was refractory to digestion by either enzyme. The same site could however be digested with MspI in DNA isolated from liver. We developed a Polymerase Chain Reaction (PCR)-based **assay** which allows us to determine whether the Ha-ras-1 **gene** promoters in DNA isolated from RMECs or liver **cells** were differentially sensitive to agents which preferentially cleave single-stranded DNA. Genomic DNAs isolated from RMECs or liver were treated with mung bean nuclease or potassium permanganate. The ability of these single-strand specific reagents to cleave the Ha-ras-1 promoter region was then assessed by measuring the efficiency with which PCR primers flanking the HpaII/MspI site in question amplified a 439 bp fragment. The results of these analyses indicated that single-strand specific reagents abrogated amplification from RMECs DNA under treatment conditions that allowed amplification of liver DNA with an efficiency of about 70% per cycle efficiency. These results are consistent with the hypothesis that in RMECs, a region of the Ha-ras promoter is involved in a topological feature (toposwitch) which renders the DNA refractory to

digestion by the HpaII and MspI enzymes. In addition to RMECs, the toposwitch was also detected in a subpopulation of lung and spleen **cells**, but not in liver or kidney **cells**. More importantly however, the loss of the toposwitch appears to play a role in NMU-induced mammary carcinogenesis. The region of the promoter containing the toposwitch became sensitive to MspI digestion in 100% of NMU induced mammary tumors, but remained refractory to digestion in 70% of DMBA-induced mammary tumors. Exposure of pubescent female rats to a carcinogenic dose of NMU initiates the in **vivo** loss of this tissue specific DNA conformation (toposwitching) in greater than 90% of RMECs of exposed animals, with a half life of about seven days. Exposure to a carcinogenic dose of dimethylbenz(a)**anthracene** (DMBA) failed to induce a detectable amount of toposwitching even at 30 days after exposure, suggesting that the latter occurs as a late spontaneous event in 30% of DMBA-indu(ABSTRACT TRUNCATED)

L21 ANSWER 22 OF 56 CANCERLIT
AN 96649123 CANCERLIT
DN 96649123
TI The detection of **gene mutation** in transgenic mice (**Muta Mouse**) following administration of known **mutagens** (Meeting abstract).
AU Brooks T M; Dean S W; Kirkland D J
CS Hazleton Europe Limited, Otley Road, Harrogate, North Yorkshire HG3 1PY, UK.
SO Environ Mol Mutagen, (1995) 25 (Suppl 25) 6.
ISSN: 0893-6692.
DT (MEETING ABSTRACTS)
LA English
FS Institute for Cell and Developmental Biology
EM 199608
ED Entered STN: 19970509
Last Updated on STN: 19970509
AB We are currently validating the **Muta Mouse** positive selection (lacZ/galE) **assay** to detect **mutation** in a tissue using known **mutagens**/carcinogens. 2-acetylaminofluorene (2-AAF) was administered as a single oral dose at 50 or 100 mg/kg and mice sacrificed 3, 7, 14, 28, 56 or 112 days after treatment. Cyclophosphamide (CPA) was dosed orally at 5 x 40 or 80 mg/kg and sampled at similar intervals. **Mutation** frequencies were determined in DNA from liver following 2-AAF and from bone marrow following CPA treatment. A **mutagenic** response was observed in mice treated at 100 mg/kg 2-AAF, seen from 28 up to 112 days after the single exposure. A small effect was seen in bone marrow following 5 x 80 mg/kg CPA treatment only at 3 days. Animals were treated with a single oral dose of N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) at 50 or 100 mg/kg or 1-chloromethylpyrene (CMP) at 25 or 50 mg/kg, and sampled 3, 7 and 10 days after treatment. Marked dose- and time-dependent increases in **mutation** frequency were seen in DNA from stomachs of MNNG-treated animals but not in CMP-treated mice. Other animals were treated topically by a single application, in acetone, of 250 or 500 ug MNNG, 5 or 10 ug CMP or 40 ug 7,12-dimethylbenz[a]**anthracene** (DMBA). Both MNNG and DMBA caused marked increases in the **mutation** frequency in DNA from treated skin, whereas only a small effect was seen with CMP. These data further demonstrate the potential of such **assay** systems for the measurement of **gene mutation** induced in **vivo** by direct and indirect-acting **mutagens**.

L21 ANSWER 17 OF 56 MEDLINE
AN 91000223 MEDLINE
DN 91000223 PubMed ID: 2119594
TI Relationship between chemically induced Ha-ras **mutation** and transformation of BALB/c 3T3 **cells**: evidence for chemical-specific activation and **cell** type-specific recruitment of oncogene in transformation.
AU Nakazawa H; Aguelon A M; Yamasaki H
CS International Agency for Research on Cancer, Lyon, France.
NC RO1 CA40534 (NCI)
SO MOLECULAR CARCINOGENESIS, (1990) 3 (4) 202-9.
Journal code: 8811105. ISSN: 0899-1987.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199011
ED Entered STN: 19910117
Last Updated on STN: 19970203
Entered Medline: 19901105
AB BALB/c 3T3 **cells** were exposed to 7,12-dimethylbenz[a] **anthracene** (DMBA) and resultant transformed foci were analyzed for the presence of A182----T **mutation** at codon 61 of Ha-ras (a **mutation** found in many DMBA-induced animal tumors). None of the 30 independently cloned transformed **cell** lines contained such a **mutation**. In order to see whether DMBA is able to induce this **mutation** in BALB/c 3T3 **cells**, we developed a method sensitive enough to detect this specific **mutation** at the frequency of 10(-6). Employing this **assay**, we found time- and dose-dependent induction by DMBA of Ha-ras A182----T **mutation** in BALB/c 3T3 **cells**; for example, 2 wk after exposure to 100 micrograms/mL DMBA, 1.4 in 1 X 10(4) **cells** contained this specific **mutation**. On the other hand, other agents that also induce BALB/c 3T3 **cell** transformation, such as 3-methylcholanthrene (MCA), 12-O-tetradecanoylphorbol-13-acetate (TPA), N-methyl-N'-nitro-N-nitrosoguanidine (MNNG), or ultraviolet light, did not induce the **mutation** at detectable frequency (less than 10(-6)). These results suggest that DMBA efficiently induces Ha-ras **mutation** in BALB/c 3T3 **cells** but that this **mutation** is not recruited in the process of **cell** transformation. A hypothesis of carcinogen-specific **mutation** of Ha-ras **gene** and its tissue (**cell** type)-specific recruitment in carcinogenesis is proposed.

L21 ANSWER 15 OF 56 MEDLINE
AN 92335305 MEDLINE
DN 92335305 PubMed ID: 1352887
TI Detection of **mutant** Ha-ras genes in chemically initiated **mouse** skin epidermis before the development of benign tumors.
CM Erratum in: Proc Natl Acad Sci U S A 1993 Jan 15;90(2):781
AU Nelson M A; Futscher B W; Kinsella T; Wymer J; Bowden G T
CS Department of Radiation Oncology, College of Medicine, University of Arizona, Tucson 85724.
NC CA 40584 (NCI)
ES05533-01 (NIEHS)
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1992 Jul 15) 89 (14) 6398-402.
Journal code: 7505876. ISSN: 0027-8424.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199208
ED Entered STN: 19920904
Last Updated on STN: 19950206
Entered Medline: 19920818
AB An activated Ha-ras oncogene has been consistently found in chemically initiated benign and malignant **mouse** skin tumors, and an activated ras oncogene has been shown to initiate the process of **mouse** skin carcinogenesis. However, the exact timing of **mutational** activation of the Ha-ras **gene** relative to application of the chemical carcinogen is not known. A sensitive **mutation**-specific PCR technique was used to experimentally address the timing of Ha-ras **gene mutational** activation. This technique can detect **mutant** Ha-ras alleles in the presence of a very large excess of normal ras alleles. Activated Ha-ras genes with 61st codon A----T **mutations** were found in the epidermis of mice 1 week after topical initiation with 7,12-dimethylbenz[a]**anthracene** or urethane by using this **assay**. These results were confirmed by Xba I restriction fragment length polymorphism analysis and direct DNA sequencing. One week after initiation is 1-2 months before the appearance of benign papillomas that harbor activated Ha-ras oncogenes when the initiated mice are promoted with the tumor promoter phorbol 12-myristate 13-acetate. Our data support the hypothesis that initiated epidermal **cells** containing an activated Ha-ras **gene** can remain dormant in the skin until a tumor promoter induces regenerative hyperplasia that allows for outgrowth of these **cells** with an activated ras oncogene to give rise to a benign papilloma.

L21 ANSWER 13 OF 56 MEDLINE
AN 93196513 MEDLINE
DN 93196513 PubMed ID: 8450770
TI Detection of chemical **mutagens** using **Muta Mouse**: a transgenic **mouse** model.
AU Hoorn A J; Custer L L; Myhr B C; Brusick D; Gossen J; Vijg J
CS Hazleton Washington, Inc, Vienna, VA 22182.
SO MUTAGENESIS, (1993 Jan) 8 (1) 7-10.
Journal code: 8707812. ISSN: 0267-8357.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199304
ED Entered STN: 19930423
Last Updated on STN: 19930423
Entered Medline: 19930415
AB A transgenic **mouse** strain with a high copy number of rescuable lacZ sequences was evaluated for its effectiveness in detecting lacZ-**mutations** in selected tissues. Procarbazine, cyclophosphamide, ethylnitrosourea, 7,12-dimethylbenz[a]**anthracene** (DMBA), acrylamide and chlorambucil were tested following either single or repeated dosing regimens. Bone marrow, liver, skin and testis tissues were selected to assess as target sites for **mutation**. Bone marrow, liver and testis tissues were examined for **mutation** following exposures to ethylnitrosourea and chlorambucil. Increased **mutant** frequencies were found for both chemicals in all three tissues. Bone marrow tissue was examined for **mutation** following procarbazine, cyclophosphamide and acrylamide exposures, and skin was examined for **mutation** following dermal application of DMBA. **Mutation** induction was observed in all cases. The results obtained from this investigation demonstrate the applicability of this transgenic **mouse** as an effective model to detect and analyze **gene mutation** in selected organs including germinal tissues. Studies of organotrophic chemical **mutagens** and carcinogens are possible with this model as are studies of the susceptibility of germinal tissues to **mutagen** exposures.

L21 ANSWER 12 OF 56 MEDLINE
AN 95285522 MEDLINE
DN 95285522 PubMed ID: 7767973
TI Dose-related changes in the profile of ras **mutations** in chemically induced CD-1 **mouse** liver tumors.
AU Manam S; Shinder G A; Joslyn D J; Kraynak A R; Hammermeister C L; Leander K R; Ledwith B J; Prahalada S; van Zwieten M J; Nichols W W
CS Department of Safety Assessment, Merck Research Laboratories, West Point, PA 19486, USA.
SO CARCINOGENESIS, (1995 May) 16 (5) 1113-9.
Journal code: 8008055. ISSN: 0143-3334.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199507
ED Entered STN: 19950713
Last Updated on STN: 19950713
Entered Medline: 19950705
AB We investigated the role of dosing regimen on ras **mutations** in chemically induced CD-1 **mouse** liver tumors. The spectra of ras **gene mutations** in liver tumors that were induced by 15 daily i.p. injections of 7,12-dimethylbenz[a]**anthracene** (DMBA), 4-aminoazobenzene (AAB), N-hydroxy-2-acetylaminofluorene (N-OH-AAF) or N-nitrosodiethylamine (DEN) were compared to those previously obtained for tumors induced by a single but higher dose of each carcinogen. The principal **assay** used was a direct tumor analysis involving sequencing of polymerase chain reaction (PCR)-amplified tumor DNA; additional **mutations** that were present in only a small fraction of tumor **cells** were detected using a transfection **assay** or a PCR-engineered restriction fragment length polymorphism method. Spontaneous liver tumors had a relatively low frequency of ras **mutations**, all found in Ha-ras codon 61, and most of these **mutations** were present in only a small fraction of tumor **cells**. With the exception of multiple-dose DEN, each group of single- and multiple-dose carcinogen-induced tumors exhibited a higher frequency of ras **mutations** compared with spontaneous tumors. For AAB, N-OH-AAF and DEN, the dosing regimen was found to affect significantly the profile of ras **mutations**. For each of these carcinogens, the multiple-dose tumor group (versus single-dose group) had fewer Ki-ras and N-ras **mutations** and more tumors in which the Ha-ras codon 61 (C-->A) **mutation** was present in a large fraction of **cells**. Our results demonstrate that the dosing procedure can materially affect the pattern of ras **gene mutation** in **mouse** liver tumors.

L21 ANSWER 8 OF 56 MEDLINE
AN 1999452907 MEDLINE
DN 99452907 PubMed ID: 10521810
TI A functional and quantitative **mutational** analysis of p53 **mutations** in yeast indicates strand biases and different roles of **mutations** in DMBA- and BBN-induced tumors in rats.
CM Erratum in: Int J Cancer 2000 Mar 15;85(6):898
AU Yamamoto K; Nakata D; Tada M; Tonoki H; Nishida T; Hirai A; Ba Y; Aoyama T; Hamada J; Furuuchi K; Harada H; Hirai K; Shibahara N; Katsuoka Y; Moriuchi T
CS Division of Cell Biology, Hokkaido University School of Medicine, Sapporo, Japan.
SO INTERNATIONAL JOURNAL OF CANCER, (1999 Nov 26) 83 (5) 700-5.
Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199911
ED Entered STN: 20000111
Last Updated on STN: 20000629
Entered Medline: 19991119
AB In order to analyze the **mutational** events and to understand the biological significance of the p53 **gene** in chemical carcinogenesis, we applied a new yeast-based p53 functional **assay** to ovarian tumors induced by 7, 12-dimethylbenz[a]**anthracene** (DMBA), as well as to transitional **cell** carcinomas of the urinary bladder induced by N-butyl-N-(4-hydroxybutyl) nitrosamine (BBN) in rats. The **assay** demonstrated that 15 of 19 DMBA induced tumors harbored clonal p53 **mutations**, which is consistent with the expectations of the "clonal expansion" hypothesis. The majority of the **mutations** were purine (AG) to pyrimidine (CT) transversions (12/19) on the non-transcribed (sense) strand (NTS), which is likely to be due to depurination created by DMBA adduct formation on the NTS. In contrast, we found no pyrimidine to purine [corrected] transversion on the NTS. After cessation of BBN treatment, BBN-induced multifocal lesions in the bladder contained heterogeneous p53 **mutations** at an early stage. In the later stage, however, clonal p53 **mutations** were identified in 4 out of 7 bladders analyzed, conforming with the concept of "field cancerization". The observed base substitutions were G-->A (1/6) or C -->T transitions (2/6), and **mutations** at T (3/6) on the NTS in clonal **mutations**, together with non-clonal **mutations**, showing a preference of C-->T to G-->A (17 vs. 0). Thus, preferential repair was found in the transcribed strand of the p53 **gene**, whether modified by DMBA or by BBN carcinogens. Very similar **mutation** patterns were observed between clonal and non-clonal **mutations** in the DMBA- and BBN-induced tumors, indicating that the **rat** yeast p53 functional **assay** can be a potential tool for the characterization of in **vivo mutation** patterns of p53, when modified by chemical carcinogens.

L21 ANSWER 7 OF 56 MEDLINE
AN 1999453355 MEDLINE
DN 99453355 PubMed ID: 10521669
TI Induction of lacZ **mutation** by 7,12-dimethylbenz[a] **anthracene** in various tissues of transgenic mice.
AU Hachiya N; Yajima N; Hatakeyama S; Yuno K; Okada N; Umeda Y; Wakata A; Motohashi Y
CS Department of Public Health, Akita University School of Medicine, Hondo 1-chome, Akita, Japan.. hachiya@ipc.akita-u.ac.jp
SO MUTATION RESEARCH, (1999 Aug 18) 444 (2) 283-95.
Journal code: 0400763. ISSN: 0027-5107.
CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199910
ED Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991029
AB The induction of **gene mutations** was examined in **MutaMouse** after an intraperitoneal injection of 7, 8-dimethylbenz[a]**anthracene** (DMBA) at 20 mg/kg in a collaborative study participated by four laboratories. Although the DMBA dose used was lower than the level that has been reported to induce micronucleated erythrocytes maximally in several **mouse** strains, a killing effect appeared after day 9 of the post-treatment interval. **Mutations** in lacZ transgene were detected by the positive selection **assay** following in vitro packaging of phage lambda from the genomic DNA of the transgenic animals that survived. The **mutant** induction was evaluated in the bone marrow, liver, skin, colon, kidney, thymus, and testis 7 to 28 days after the treatment. In the bone marrow, the **mutant** frequency reached a maximum, approximately a 30-fold increase, 14 days after the treatment and the increased frequency persisted at least up to day 28 of the post-treatment. Induction of **mutants** was detected in the liver, colon, thymus, and skin to lesser extents. Marginal responses were obtained in the kidney and testis. The slight increases in the **mutant** frequencies in the kidney and testis observed in some laboratories were within laboratory-to-laboratory or animal-to-animal variations. In contrast to the **gene mutation** induction in the bone marrow, the frequency of micronucleated reticulocytes increased transiently 3 days after the treatment and returned to a control level before day 8 of the post-treatment. It was suggested that DMBA induced **gene mutation** is fixed in stem **cells** depending on **cell** proliferation while DNA damages responsible for chromosome breakage are not transmitted to progeny **cells**.

L21 ANSWER 6 OF 56 MEDLINE
AN 2000035347 MEDLINE
DN 20035347 PubMed ID: 10567037
TI Antimutagenic effects of centchroman--a contraceptive and a candidate drug for breast cancer in multiple **mutational** assays.
AU Giri A K; Mukhopadhyay A; Sun J; Hsie A W; Ray S
CS Indian Institute of Chemical Biology, 4 Raja S.C.Mullick Road, Jadavpur, Calcutta 700 032, India.. iichbio@giscl01.vsnl.net.in
SO MUTAGENESIS, (1999 Nov) 14 (6) 613-20.
Journal code: 8707812. ISSN: 0267-8357.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200003
ED Entered STN: 20000320
Last Updated on STN: 20000320
Entered Medline: 20000308
AB Centchroman (CC), a non-steroidal oral contraceptive and a candidate drug for breast cancer, has been reported to exhibit partial to complete remission of lesions in 40.5% of breast cancer patients. The potent anti-oestrogenic activity, negligible side-effects and anti-breast cancer activity of CC prompted us to evaluate the antimutagenic effects of this compound in a bacterial **mutagenicity assay** and CHO/HPRT and AS52/GPT **mutation** assays in vitro and in **vivo** in female Swiss albino mice as measured by both sister chromatid exchange (SCE) and chromosome aberrations (CA) against three known positive **mutagen** compounds, dimethylbenz[a] **anthracene** (DMBA), cyclophosphamide (CP) and mitomycin C (MMC). Antimutagenicity assays in Salmonella strains TA97a, TA100, TA98 and TA102 were carried out against commonly used known positive **mutagens**, sodium azide, 4-nitro-o-phenylenediamine, cumine hydroperoxide, 2-aminofluorene and danthron. A significantly reduced number of bacterial histidine revertant colonies was observed in the plates treated with 0.1, 1, 5 and 10 microg/plate CC and a positive compound when compared with bacterial plates treated with the respective positive compound alone. Ethyl methanesulfonate (EMS), a commonly used positive **mutagen** for CHO/HPRT and AS52/GPT **gene mutation** assays, was used for antimutagenicity **assay** in these **cells**. CC exhibited protective effects against the **mutagenicity** of EMS in these two mammalian **cell mutation** assays, CHO/HPRT and AS52/GPT. In the in **vivo** studies, pretreatment with CC reduced DMBA-induced SCE and CA and CP- and MMC-induced CA when compared with the group treated only with the positive compounds. These results indicate that CC can reduce the **mutagenic** effects of known genotoxic compounds.

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TI **Mutational** spectra for polycyclic aromatic hydrocarbons in the supF target **gene**.
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SO MUTATION RESEARCH, (2000 May 30) 450 (1-2) 75-93. Ref: 77
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CY Netherlands
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200007
ED Entered STN: 20000810
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AB An SV40-based shuttle vector system was used to identify the types of **mutational** changes and the sites of **mutation** within the supF DNA sequence generated by the four stereoisomers of benzo[c]phenanthrene 3,4-dihydrodiol 1,2-epoxide (B[c]PhDE), by racemic mixtures of bay or fjord region dihydrodiol epoxides (DE) of 5-methylchrysene, of 5, 6-dimethylchrysene, of benzo[g]chrysene and of 7-methylbenz[a]**anthracene** and by two direct acting polycyclic aromatic hydrocarbon carcinogens, 7-bromomethylbenz[a]**anthracene** (7-BrMeBA) and 7-bromomethyl-12-methylbenz[a]**anthracene** (7-BrMe-12-MeBA). The results of these studies demonstrated that the predominant type of **mutation** induced by these compounds is the base substitution. The chemical preference for reaction at deoxyadenosine (dAdo) or deoxyguanosine (dGuo) residues in DNA, which is in general correlated with the spatial structure (planar or non-planar) of the reactive polycyclic aromatic hydrocarbon, is reflected in the preference for **mutation** at A&z.ccirf;T or G&z.ccirf;C pairs. In addition, if the ability to react with DNA in **vivo** is taken into account, the relative **mutagenic** potencies of the B[c]PhDE stereoisomers are consistent with the higher tumorigenic activity associated with non-planar polycyclic aromatic hydrocarbons and their extensive reaction with dAdo residues in DNA. Comparison of the types of **mutations** generated by polycyclic aromatic hydrocarbons and other bulky carcinogens in this shuttle vector system suggests that all bulky lesions may be processed by a similar mechanism related to that involved in replication past apurinic sites. However, inspection of the distribution of **mutations** over the target **gene** induced by the different compounds demonstrated that individual polycyclic aromatic hydrocarbons induce unique patterns of **mutational** hotspots within the target **gene**. A polymerase arrest **assay** was used to determine the sequence specificity of the interaction of reactive polycyclic aromatic hydrocarbons with the shuttle vector DNA. The results of these assays revealed a divergence between **mutational** hotspots and polymerase arrest sites for all compounds investigated, i.e., sites of **mutational** hotspots do not correspond to sites where high levels of adduct formation occur, and suggested that some association between specific adducts and sequence context may be required to constitute a premutagenic lesion. A site-specific **mutagenesis** system employing a single-stranded vector (M13mp7L2) was used to investigate the **mutational** events a single benzo[a]pyrene or benzo[c]phenanthrene dihydrodiol epoxide-DNA adduct elicits within specific sequence contexts.

These studies showed that sequence context can cause striking differences in **mutagenic** frequencies for given adducts. In addition, these sequence context effects do not originate only from nucleotides immediately adjacent to the adduct, but are also modulated by more distal nucleotides. The implications of these results for mechanisms of polycyclic aromatic hydrocarbon-induced **mutagenesis** and carcinogenesis are discussed.

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TI **Mutant** frequency and molecular analysis of in **vivo** lacI **mutations** in the bone marrow of Big Blue rats treated with 7, 12-dimethylbenz[a]**anthracene**.
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LA English
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AB Recently, we evaluated lacI **mutations** in lymphocytes and mammary tissue of Big Blue (BB) rats exposed to 7, 12-dimethylbenz[a] **anthracene** (DMBA). The results on the time course of **mutant** induction suggested that the lacI **gene** may manifest a tissue-specific increase in **mutant** frequency (MF). To test whether a tissue-specific increase in lacI MF is dependent on the **cell** proliferation rate of a tissue, we examined rapidly proliferating bone marrow **cells** for DMBA-induced lacI **mutations**. Seven-week-old female BB rats were given single doses of 0, 20, and 130 mg/kg DMBA by gavage and the lacI MFs in the bone marrow were measured over a period of 14 weeks following treatment. Bone marrow **cells** had a remarkably low average background MF (3.1 +/- 1.6 x 10(-6) plaque-forming units) and the DMBA-induced lacI MFs were significantly higher than control MFs for both doses and at all time points ($P < 0.01$). The lacI MF in the bone marrow increased for 2 weeks and then remained relatively constant; 20 and 130 mg/kg DMBA produced 34- and 106-fold increases in MF over control MF. DNA sequencing revealed that the majority of DMBA-induced lacI **mutations** were base-pair substitutions and that A:T --> T:A (48%) and G:C --> T:A (24%) transversions were the predominant types. Thus, the different lacI **mutation** fixation times observed for bone marrow (2 weeks), mammary (10 weeks), and lymphocytes (6 weeks) suggest that the lacI **gene** manifests a tissue-specific **mutation** fixation time, which may depend on the **cell** proliferation rate of a tissue. In addition, the relatively low spontaneous MF in bone marrow compared with that in other tissues may be useful for increasing the sensitivity of the **assay** for detecting induced MFs in BB rats.

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DN 20584309 PubMed ID: 11152561
TI 7,12-dimethylbenz[a]**anthracene**-induced **mutation** in the Tk **gene** of Tk(+/-) mice: automated scoring of lymphocyte clones using a fluorescent viability indicator.
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AB 7,12-Dimethylbenz[a]**anthracene** (DMBA) is a rodent carcinogen and a potent in **vivo mutagen** for the X-linked hypoxanthine guanine phosphoribosyl transferase (hprt) **gene** of rats and for the lacI transgene of Big Blue mice and rats. Although DMBA is also a powerful clastogen, molecular analysis of these DMBA-induced hprt and lacI **mutations** indicates that most are single base-pair (bp) substitutions and 1- to 3-bp frameshifts. In the present study, we evaluated the types of **mutations** induced by DMBA in the autosomal thymidine kinase (Tk) **gene** of Tk(+/-) mice. Male and female 5- to 6-week-old animals were injected i.p. with DMBA at a dose of 30 mg/kg. Five weeks after the treatment, hprt and Tk **mutant** frequencies were determined using a limiting dilution clonal **assay** in 96-well plates. We established conditions for the automated identification of wells containing expanded lymphocyte clones using the fluorescent indicator alamarBlue. This procedure allowed the unbiased identification of viable clones and calculation of **mutant** frequencies. In male mice, DMBA treatment increased the frequency of hprt **mutants** from 1.8 +/- 1.1 to 34 +/- 9 x 10(-6), and Tk **mutants** from 33 +/- 12 to 78 +/- 26 x 10(-6); treated female mice had a significant but lower increase in hprt **mutant** frequency than did males. Molecular analysis of DMBA-induced Tk **mutants** revealed that at least 75% had the entire wild-type Tk allele missing. The results indicate that the predominant types of DMBA-induced **mutation** detected by the autosomal Tk **gene** are different from those detected by the X-linked hprt **gene**. The Tk **gene** mainly detects loss of heterozygosity **mutation**, whereas the majority of **mutations** previously found in the hprt **gene** were point **mutations**.